```
ΑN
     2003:696700 CAPLUS
     139:219341
DN
ΤI
     DNA-binding amide-drug conjugates
IN
     Szekely, Zoltan; Hariprakasha, Humcha Krishnamurthy; Cholody, Marek W.;
     Michejda, Christopher J.
     The Government of the United States of America, Representated by the
PA
     Secretary Department of Health and Human Services, USA
     PCT Int. Appl., 50 pp.
SO
     CODEN: PIXXD2
DT
     Patent
     English
LA
FAN.CNT 1
     PATENT NO.
                      KIND
                            DATE
                                           APPLICATION NO.
                                                            DATE
                            20030904
                                           WO 2003-US6006
PΙ
     WO 2003072058
                       A2
                                                             20030227
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD,
             RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
             NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
             ML, MR, NE, SN, TD, TG
PRAI US 2002-361050P
                            20020227
                      P
     US 2002-370168P
                       Ρ
                            20020405
OS
     MARPAT 139:219341
AΒ
    An amide conjugate comprising a DNA intercalator binds to the minor
groove
     of DNA. A compn. comprising the conjugate and a carrier is useful for
     treating cancer in a mammal. Thus, 1-(chloromethyl)-5-hydroxy-1,2-
dihydro-
     3H-benz[e]indole-8-carboxylic acid (CBIr), a rigid DNA alkylator, was
     prepd. and conjugated to an imidazole-contq. deriv.
     591248-06-5P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT
     (Reactant or reagent)
        (DNA alkylator; DNA-binding polyamide drug conjugates)
RN
     591248-06-5 CAPLUS
     1H-Benz[e]indole-8-carboxylic acid, 1-(chloromethyl)-2,3-dihydro-5-
hydroxy-
      (9CI)
            (CA INDEX NAME)
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ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN

L4

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IT
     591248-27-0
```

RL: RCT (Reactant); RACT (Reactant or reagent) (DNA-binding polyamide drug conjugates)

RN591248-27-0 CAPLUS

CN 3H-Benz[e]indole-3-carboxylic acid, 8-[(1H-benzotriazol-1yloxy)carbonyl]-

1-(chloromethyl)-1,2-dihydro-5-hydroxy-, 9H-fluoren-9-ylmethyl ester (9CI)

(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

IT 591247-86-8P 591247-87-9P 591247-88-0P 591247-89-1P 591247-90-4P 591247-91-5P

591247-92-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);

RACT

(Reactant or reagent)

(in dihydrobenzindolecarboxylic acids prepn.; DNA-binding polyamide drug conjugates)

RN591247-86-8 CAPLUS

CN 3H-Benz[e]indole-3,8-dicarboxylic acid, 1,2-dihydro-5-(phenylmethoxy)-1-[[(2,2,6,6-tetramethyl-1-piperidinyl)oxy]methyl]-, 3-(1,1-dimethylethyl) 8-(phenylmethyl) ester (9CI) (CA INDEX NAME)

RN 591247-87-9 CAPLUS

CN 3H-Benz[e]indole-3,8-dicarboxylic acid, 1,2-dihydro-5-(phenylmethoxy)-1[[(2,2,6,6-tetramethyl-1-piperidinyl)oxy]methyl]-, 3-(9H-fluoren-9ylmethyl) 8-(phenylmethyl) ester (9CI) (CA INDEX NAME)

RN 591247-88-0 CAPLUS

CN 3H-Benz[e]indole-3,8-dicarboxylic acid, 1,2-dihydro-1-(hydroxymethyl)-5-(phenylmethoxy)-, 3-(9H-fluoren-9-ylmethyl) 8-(phenylmethyl) ester (9CI) (CA INDEX NAME)

RN 591247-89-1 CAPLUS

CN 3H-Benz[e]indole-3,8-dicarboxylic acid, 1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1,2-dihydro-5-(phenylmethoxy)-, 3-(9H-fluoren-9-ylmethyl) 8-(phenylmethyl) ester (9CI) (CA INDEX NAME)

RN 591247-90-4 CAPLUS

CN 3H-Benz[e]indole-3,8-dicarboxylic acid, 1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1,2-dihydro-5-hydroxy-, 3-(9H-fluoren-9-ylmethyl) ester (9CI) (CA INDEX NAME)

RN 591247-91-5 CAPLUS

CN 3H-Benz[e]indole-3,8-dicarboxylic acid, 5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[[[(1,1-

dimethylethyl)dimethylsilyl]oxy

]methyl]-1,2-dihydro-, 3-(9H-fluoren-9-ylmethyl) ester (9CI) (CA INDEX NAME)

RN 591247-92-6 CAPLUS

CN 3H-Benz[e]indole-3-carboxylic acid, 8-[(1H-benzotriazol-1-yloxy)carbonyl]-

5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1,2-dihydro-, 9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

PAGE 2-A

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2001:627681 CAPLUS

DN 135:338739

TI Metal cation complexation and activation of reversed CPyI analogues of CC-1065 and duocarmycin SA: partitioning the effects of binding and catalysis

AU Ellis, David A.; Wolkenberg, Scott E.; Boger, Dale L.

CS Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

SO Journal of the American Chemical Society (2001), 123(38), 9299-9306 CODEN: JACSAT; ISSN: 0002-7863

PB American Chemical Society

DT Journal

LA English

AB The synthesis and examn. of a novel class of reversed CPyI analogs of CC-1065 and the duocarmycins are described. Capable of a unique metal cation activation of DNA alkylation, these agents allowed the effects of the DNA binding domain (104-fold increase in DNA alkylation rate and efficiency) to be partitioned into two components: that derived from enhanced DNA binding affinity and selectivity (10-80-fold) and that derived from a contribution to catalysis (250-5000-fold). In addn., the reversed enantiomeric selectivity of these sequence selective DNA alkylating agents provides further strong support for a previously disclosed model where it is the noncovalent binding selectivity of the compds., and not the alkylation subunit or the source of catalysis, that controls the DNA alkylation selectivity.

IT 371248-89-4

RL: PRP (Properties)

(metal cation complexation and activation of reversed CPyI analogs of CC-1065 and duocarmycin SA)

RN 371248-89-4 CAPLUS

CN 3H-Benz[e]indole-3,8-dicarboxylic acid, 1-(chloromethyl)-1,2-dihydro-5-(phenylmethoxy)-, 3-(1,1-dimethylethyl) ester, (1R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 371248-78-1P

RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(metal cation complexation and activation of reversed CPyI analogs of CC-1065 and duocarmycin SA)

RN 371248-78-1 CAPLUS

CN 3H-Benz[e]indole-3,8-dicarboxylic acid, 1-(chloromethyl)-1,2-dihydro-5-(phenylmethoxy)-, 3-(1,1-dimethylethyl) ester, (1S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 371248-77-0

RL: RCT (Reactant); RACT (Reactant or reagent)

(metal cation complexation and activation of reversed CPyI analogs of CC-1065 and duocarmycin SA)

RN 371248-77-0 CAPLUS

CN 3H-Benz[e]indole-3,8-dicarboxylic acid, 1-(chloromethyl)-1,2-dihydro-5-(phenylmethoxy)-, 3-(1,1-dimethylethyl) 8-methyl ester, (1S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2001:172344 CAPLUS

DN 134:340376

TI Synthesis, Chemical Properties, and Biological Evaluation of CC-1065 and Duocarmycin Analogues Incorporating the 5-Methoxycarbonyl-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one Alkylation Subunit

AU Boger, Dale L.; Hughes, Terry V.; Hedrick, Michael P.

CS Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

SO Journal of Organic Chemistry (2001), 66(7), 2207-2216 CODEN: JOCEAH; ISSN: 0022-3263

PB American Chemical Society

DT Journal

LA English

OS CASREACT 134:340376

GI

AB The synthesis of 5-methoxycarbonyl-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]

indol-4-one (C5-CO2Me-CBI), a substituted CBI deriv. bearing a C5 methoxycarbonyl group, and its corresponding 5-hydroxymethyl deriv. are described in efforts to establish substituent electronic effects on the agents' functional reactivity and the resulting effect this has on their rate of DNA alkylation. Resoln. of an immediate C5-CO2Me-CBI precursor and its incorporation into both enantiomers of analogs of the duocarmycins

are also detailed. A study of the solvolysis reactivity and regionelectivity of N-BOC-C5-CO2Me-CBI (12) revealed that the introduction  ${\sf N}$ 

of a C5 Me ester modestly slowed the rate of solvolysis (1.8.times., pH 3)

without altering the inherent reaction regionselectivity (>20:1). The comparison of the X-ray structures of the N-CO2Me derivs. of C5-CO2Me-CBI

and CBI revealed correlations with the reaction regioselectivity and the relative reactivity of the compds. The latter correlated well with the less reactive C5-CO2Me-CBI exhibiting a shortened N2-C2a bond length (1.386 vs 1.390 .ANG.) and smaller .chi.1 dihedral angle (8.1.degree. vs 21.2.degree.) indicative of greater vinylogous amide conjugation and was accompanied by a diminished (cross-conjugated) cyclopropane conjugation (shorter bond lengths). Establishment of the DNA alkyation properties revealed that C5-CO2Me-CBI-based agents retained the identical alkylation

selectivity of the natural products. More importantly, the C5 Me ester was found to decrease the rate (0.77. times.) of DNA alkylation relative to

CBI, consistent with its inherent lower reactivity. These results indicate that the previously obsd. increase in the rate of DNA alkylation

for C7-substituted CBI analogs including CCBI (7-cyano-CBI) is contrary

to

or

expectations based on their inherent reactivities. Unlike (I), in which the C5 Me ester does not bind in the minor groove, the C7 substituent lies

in the minor groove extending the rigid length of the agents, further enhancing the DNA binding-induced conformational change responsible for activation toward nucleophilic attack and catalysis of the DNA alkylation

reaction.

## IT 337465-84-6P 337465-94-8P

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity

effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(synthesis, chem. properties, and biol. evaluation of CC-1065 and duocarmycin analogs incorporating the 5-methoxycarbonyl-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one alkylation subunit)

RN 337465-84-6 CAPLUS

CN 1H-Benz[e]indole-6-carboxylic acid, 1-(chloromethyl)-2,3-dihydro-5-hydroxy-

3-[(5,6,7-trimethoxy-lH-indol-2-yl)carbonyl]-, methyl ester, (1S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

RN 337465-94-8 CAPLUS

CN 1H-Benz[e]indole-6-carboxylic acid, 1-(chloromethyl)-2,3-dihydro-5-hydroxy-

3-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (1R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

### IT 337465-81-3P 337465-91-5P

or

RL: PEP (Physical, engineering or chemical process); PUR (Purification

recovery); RCT (Reactant); SPN (Synthetic preparation); PREP

Absolute stereochemistry. Rotation (-).

RN 337465-91-5 CAPLUS

CN 3H-Benz[e]indole-3,6-dicarboxylic acid, 1-(chloromethyl)-1,2-dihydro-5-(methoxymethoxy)-, 3-(1,1-dimethylethyl) 6-methyl ester, (1R)- (9CI)

(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

#### IT 337465-87-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)

(synthesis, chem. properties, and biol. evaluation of CC-1065 and duocarmycin analogs incorporating the 5-methoxycarbonyl-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one alkylation subunit)

RN 337465-87-9 CAPLUS

CN 3H-Benz[e]indole-3,6-dicarboxylic acid, 1-(chloromethyl)-1,2-dihydro-5-hydroxy-, dimethyl ester, (1S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

## IT 337465-86-8P

RL: SPN (Synthetic preparation); PREP (Preparation) (synthesis, chem. properties, and biol. evaluation of CC-1065 and duocarmycin analogs incorporating the 5-methoxycarbonyl-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one alkylation subunit)

RN 337465-86-8 CAPLUS

CN 3H-Benz[e]indole-3,6-dicarboxylic acid, 1,2-dihydro-5-hydroxy-1-(methoxymethyl)-, 3-(1,1-dimethylethyl) 6-methyl ester, (1S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

# Reference(s):

### L7 ANSWER 3 OF 10 BEILSTEIN COPYRIGHT 2003 BEILSTEIN CDS MDL on STN

Beilstein Records (BRN): 8811703

Chemical Name (CN): 3-(5,6,7-trimethoxyindol-2-carbonyl)-1-

(chloromethyl)-5-hydroxy-6-

methoxycarbonyl-

1,2-dihydro-3H-benz<e>indole
Autonom Name (AUN): 1-chloromethyl-5-hydroxy-3-(

1-chloromethyl-5-hydroxy-3-(5,6,7trimethoxy-1H-indole-2-carbonyl)-2,3dihydro-1H-benzo<e>indole-6-carboxylic

acid methyl ester

Molec. Formula (MF): C27 H25 Cl N2 O7

Molecular Weight (MW): 524.96

Lawson Number (LN): 26860, 26736, 289

Compound Type (CTYPE): heterocyclic

Constitution ID (CONSID): 7459350
Tautomer ID (TAUTID): 8293792
Entry Date (DED): 2001/07/25
Update Date (DUPD): 2001/07/25

Reference(s):

# Reference(s):

# Reference(s):

CM 2

FBRN 1098214 FMF Cl H

## Reference(s):

### L7 ANSWER 7 OF 10 BEILSTEIN COPYRIGHT 2003 BEILSTEIN CDS MDL on STN

Beilstein Records (BRN): 8800356

Chemical Name (CN): (+)-(1R)-3-(tert-butyloxycarbonyl)-1-

chloromethyl-6-methoxycarbonyl-5-(methoxymethoxy)-1,2-dihydro-3H-

benz<e>indole

Autonom Name (AUN): 1-chloromethyl-5-methoxymethoxy-1,2-

dihydro-benzo<e>indole-3,6-dicarboxylic acid 3-tert-butyl ester 6-methyl ester

Molec. Formula (MF): C22 H26 Cl N O6

Molecular Weight (MW): 435.90

Lawson Number (LN): 26736, 1762, 689, 318, 289

File Segment (FS): Stereo compound Compound Type (CTYPE): heterocyclic

Constitution ID (CONSID): 7448796
Tautomer ID (TAUTID): 8273532
Entry Date (DED): 2001/07/25
Update Date (DUPD): 2001/07/25

### Reference(s):

## L7 ANSWER 8 OF 10 BEILSTEIN COPYRIGHT 2003 BEILSTEIN CDS MDL on STN

Beilstein Records (BRN): 8800355

Chemical Name (CN): (-)-(1S)-3-(tert-butyloxycarbonyl)-1-

chloromethyl-6-methoxycarbonyl-5-(methoxymethoxy)-1,2-dihydro-3H-

benz<e>indole

Autonom Name (AUN): 1-chloromethyl-5-methoxymethoxy-1,2-

dihydro-benzo<e>indole-3,6-dicarboxylic
acid 3-tert-butyl ester 6-methyl ester

Molec. Formula (MF): C22 H26 Cl N O6

Molecular Weight (MW): 435.90

Lawson Number (LN): 26736, 1762, 689, 318, 289

File Segment (FS): Stereo compound Compound Type (CTYPE): heterocyclic

Constitution ID (CONSID): 7448796
Tautomer ID (TAUTID): 8273532
Entry Date (DED): 2001/07/25
Update Date (DUPD): 2001/07/25

## Reference(s):

### L7 ANSWER 9 OF 10 BEILSTEIN COPYRIGHT 2003 BEILSTEIN CDS MDL on STN

8798815

Beilstein Records (BRN):

Chemical Name (CN): 3-(tert-butyloxycarbonyl)-1-

(chloromethyl) -

6-methoxycarbonyl-5-(methoxymethoxy)-

1,2-

Autonom Name (AUN):

1-chloromethyl-5-methoxymethoxy-1,2-dihydro-benzo<e>indole-3,6-dicarboxylic acid 3-tert-butyl ester 6-methyl ester c22 H26 Cl N O6

dihydro-3H-benz<e>indole

Molec. Formula (MF):
Molecular Weight (MW):
Lawson Number (LN):
Compound Type (CTYPE):
Constitution ID (CONSID):
Tautomer ID (TAUTID):
Entry Date (DED):
Update Date (DUPD):

435.90 26736, 1762, 689, 318, 289 heterocyclic 7448796 8273532 2001/07/25 2001/07/25

Reference(s):

### L7 ANSWER 10 OF 10 BEILSTEIN COPYRIGHT 2003 BEILSTEIN CDS MDL on STN

Beilstein Records (BRN): 8792003

Chemical Name (CN): 1-(chloromethyl)-5-hydroxy-3-

methoxycarbonyl-6-methoxycarbonyl-1,2-

dihydro-3H-benz<e>indole

Autonom Name (AUN): 1-chloromethyl-5-hydroxy-1,2-dihydro-

benzo<e>indole-3,6-dicarboxylic acid

dimethyl ester

Molec. Formula (MF): C17 H16 C1 N O5

Molecular Weight (MW): 349.77

Lawson Number (LN): 26736, 1762, 289

Compound Type (CTYPE): heterocyclic

Constitution ID (CONSID): 7442995
Tautomer ID (TAUTID): 8280273
Entry Date (DED): 2001/07/25
Update Date (DUPD): 2001/07/25

### Reference(s):

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Structure attributes must be viewed using STN Express query preparation.

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FILE 'REGISTRY' ENTERED AT 18:12:33 ON 13 OCT 2003

L1STRUCTURE UPLOADED

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G2 C, N

L7

18 S L1 FUL L3

FILE 'CAPLUS' ENTERED AT 18:12:54 ON 13 OCT 2003

3 S L3 L4

FILE 'BEILSTEIN' ENTERED AT 18:13:25 ON 13 OCT 2003

L5 0 S L1 L6 10 S L1 FUL 10 S L6 NOT L4

FILE 'MARPAT' ENTERED AT 18:14:24 ON 13 OCT 2003

L80 S L1 30 S L1 FUL L9

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	105.75	511.35
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-1.95

STN INTERNATIONAL LOGOFF AT 18:16:40 ON 13 OCT 2003